

NONTECHNICAL ABSTRACT

No consistently effective therapy exists for metastatic renal cell carcinoma (RCC). Currently, only 2% of patients with advanced RCC live five years following diagnosis. Interest in immunotherapy for RCC has been stimulated by the observation of spontaneous, short-term regressions of metastases without treatment in up to 1%-3% of patients. We have conducted extensive laboratory studies using a new strategy for inducing anti-tumor immune responses to mouse tumors including RCC. By inserting immunostimulatory genes into mouse RCC tumor cells, and injecting them under the skin, systemic antitumor immune responses have been reproducibly induced, resulting in eradication of small amounts of implanted tumor at distant sites. The Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF) gene in these model studies conferred the most potent antitumor effects. Efficient introduction of this gene in the model cancer vaccine cells was accomplished with the retroviral vector MFG. This efficiency made feasible the generation of genetically engineered human cancer vaccines. Using the MFG vector, we were able to prepare kidney cancer cell vaccines from 20 of 22 cases in a preliminary study. Such transduced cells secrete 10 to 50 fold more GM-CSF than cultured, non-transduced RCC cells.

Lethal irradiation of the genetically engineered RCC cells did not diminish therapeutic effects of vaccine cells genetically engineered to secrete the GM-CSF gene in our mouse studies. Irradiation of tumor vaccines affords a measure of safety for human studies without compromising potential therapeutic efficacy. Otherwise, patients might have to be injected with live genetically engineered cancer cells for treatment. To develop this new strategy for the treatment of human cancer, safety of tumor vaccines produced by our procedure must be established in a phase I (toxicity) study.

The overall objective of this phase I study is to evaluate the safety and tolerability of RCC vaccine cell skin injections using a vaccine derived from a patient's RCC cells prepared either with or without human GM-CSF gene transfer. To help ensure safety, all tumor cell vaccines will be irradiated prior to injection. For evaluation of toxicities both from cancer vaccine cells alone, as well as from GM-CSF gene transfer, the trial will have two dose escalating studies within it. In one arm of the study, advanced kidney cancer patients will be treated with irradiated cells prepared without GM-CSF gene transfer. In the other arm of the study, patients will be treated with escalating doses of irradiated RCC cells transduced with the human GM-CSF gene. Patients will be randomly assigned to each arm. In all cases, surgical removal of the kidney will provide the source of the vaccine cells. The patients to be enrolled in this study will have greater than 1 billion cancer cells in their bodies as evidenced by the presence of visible metastases on X-rays. Unfortunately, the mouse RCC genetically engineered tumor vaccines were effective at eliminating up to about 10,000 cancer cells at distant sites. While it may be unlikely that the injections will benefit each patient enrolled in this trial with advanced disease, if safety can be established for these procedures, future studies involving larger number of RCC patients with occult metastases could be conducted.